CHAPTER 3

# Bioactive Compounds of Tomatoes as Health Promoters

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**Abstract:** Tomato (*Lycopersicon esculentum* Mill.) is one of the most consumed vegetables in the world and probably the most preferred garden crop. It is a key component of the Mediterranean diet, commonly associated with a reduced risk of chronic degenerative diseases. Currently there are a large number of tomato cultivars with different morphological and sensorial characteristics and tomato-based products, being major sources of nourishment for the world's population. Its consumption brings health benefits, linked with its high levels of bioactive ingredients. The main compounds are carotenoids such as β-carotene, a precursor of vitamin A, and mostly lycopene, which is responsible for the red colour, vitamins in particular ascorbic acid and tocopherols, phenolic compounds including hydroxycinnamic acid derivatives and flavonoids, and lectins. The content of these compounds is variety dependent. Besides, unlike unripe tomatoes, which contain a high content of tomatine (glycoalkaloid) but no lycopene, ripe red tomatoes contain high amounts of lycopene and a lower quantity of glycoalkaloids. Current studies demonstrate the several benefits of these bioactive compounds, either isolated or in combined extracts, namely anticarcinogenic, cardioprotective and hepatoprotective effects among other health benefits, mainly due to its antioxidant and anti-inflammatory properties. The chemistry, bioavailability and bioactivity of these bioactive compounds will be discussed, as well as the main mechanisms of action against cancer and other bioactivities including antioxidant, anti-inflammatory, cardiovascular and hepatoprotective effects in humans. Possible applications of tomato bioactive compounds in the industry will also be proposed.

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## INTRODUCTION

The tomato plant (*Lycopersicon esculentum* Mill.) was imported from the Andean region to Europe in the 16$^{th}$ century. It belongs to the Solanaceae family that includes many other plants of economic importance, including potatoes, eggplants, peppers and tobacco [1]. Today, this species is widespread throughout the world, representing the most economically important vegetable crop worldwide. In fact, tomato is the most consumed vegetable after potatoes and probably the most preferred garden crop. In 2013, about 164 million tonnes of tomatoes were produced in the world, having been registered an increase above 2.6 million tonnes over 2012. The three main producing countries are China, India and United States of America, but it is in the Mediterranean and Arabian countries that their consumption is higher [2].

Tomato is a very versatile fruit, being consumed fresh but also processed as paste, soup, juice, sauce, powder, or concentrate. In addition, there are several tomato cultivars and varieties with a wide range of morphological and sensorial characteristics which affect the way how they are prepared and consumed [1, 3, 4]. Tomatoes and tomato-based food products are an important source of nourishment for the world's population. Regarding its nutritional value, if one takes into consideration only the proteins, fat, carbohydrates, or sugars content, it appears clearly that it does not have a high nutritional value. However, it represents an important source of other nutrients and non-nutrients endowed with important health promoting properties, namely carotenoids such as β-carotene (provitamin A) and mostly lycopene, which provides the deep red colour, vitamins such as ascorbic acid (vitamin C) and tocopherols (vitamin E), phenolic compounds including hydroxycinnamic acid derivatives and flavonoids, lectins, and minerals (K, Mn, Ca, Cu and Zn) [3 - 5].

Tomatoes are the most important component of the Mediterranean diet, known to be beneficial for human health [6]. A relationship between the consumption of tomatoes and tomato-based foods and the prevention of chronic degenerative disease induced by oxidative stress and inflammation has been indicated in several studies [7 - 10]. However, the bioaccessibility and bioavailability of tomato compounds is affected by the way how tomatoes are consumed (*i.e.*, raw or processed), which affects its subsequent bioactivity. Clinical trials performed in the last years elucidate the positive effects and mechanisms involved in the activity of tomato compounds against cardiovascular disease and various types of cancer [9 - 12]. Indeed, tomato extracts, as well as lycopene, α-tomatine and some phenolic compounds have been highlighted as having increased potential for the development of new drugs, nutraceuticals and functional foods.

This chapter highlights the tomato fruit as a functional food and as a source of nutraceutical ingredients of industrial value. In this sense, the major health promoting compounds of tomatoes are described chemically and their bio-availability, bioactivity and impact on human health are discussed. Recent *in vitro* and *in vivo* clinical trials are presented, with particular attention paid to the mechanisms behind the protective effects of tomato bioactive compounds against the most common degenerative diseases associated to oxidative stress and inflammation, including cardiovascular and hepatocellular diseases, diabetes and various types of cancer, among other health problems.

## TOMATO BIOACTIVE COMPOUNDS

Nowadays, consumers are increasingly made aware and better informed about the health benefits provided by food beyond its basic nutritional role. Actually, they are looking for foods with health promoting properties called “functional foods”. The tomato fruit is a good example, whose functionality or health claim properties are conferred by biologically active ingredients responsible for decreasing the risk of susceptibility to certain diseases. The major compounds of this fruit (Fig. **1**) are carotenoids (β-carotene and mainly lycopene), vitamins (ascorbic acid and tocopherols), and phenolic compounds including hydrocinnamic acids (mainly caffeic acid and its ester chlorogenic acid) and flavonoids such as narigenin and rutin [4, 5, 13]. Other bioactive compounds, such as glycoalkaloids and lectins

also present in tomato fruits have shown relevant biological effects *in vitro* and *in vivo* [14, 15]. Nevertheless, the content of bioactive compounds in tomatoes is affected by environmental and genetic (cultivar or variety) factors, geographical location, agricultural practices, processing conditions, among others [4, 16 - 20]. The main bioactive compounds of tomato fruit are described below.

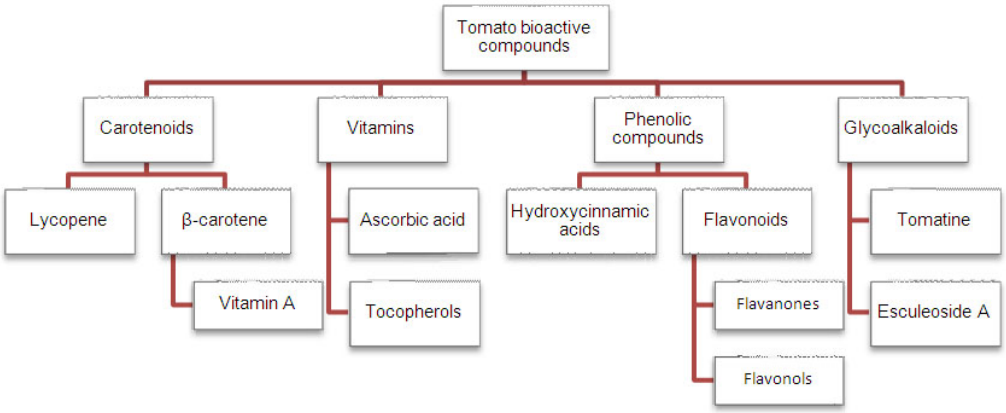


**Fig. (1).** Groups of bioactive compounds of tomatoes.

## Carotenoids

Carotenoids are a class of hydrocarbons consisting of eight isoprene units, which are joined in a head-to-tail pattern (except at the centre) to confer symmetry to the molecular structure. This way, the two central methyl groups are in a 1,6-positional relationship and the remaining non-terminal methyl groups are in a 1,5-positional relationship. Most carotenoids derive from a 40-carbon polyene chain structure, which is considered as the backbone of these compounds. This chain can terminate with cyclic end-groups (rings) and may have oxygen-containing functional groups. The long unsaturated alkyl chains make carotenoids highly lipophilic molecules. In higher plants, carotenoids can be found in chloroplasts of photosynthetic tissues and in chromoplasts of flowers and fruits. Generally, they occur in the free form in leaves and in the esterified form in other tissues. These natural pigments play a central role in photosynthesis; they are involved in photosystem assembly and light harvesting, and protect from excessive light through energy dissipation and free radical elimination, thereby reducing membrane damage. In humans, carotenoids are part of the antioxidant defence

system and interact synergistically with other bioactive compounds [21]. Once animals cannot synthesize carotenoids, they need to be incorporated through diet, being tomatoes and tomato based-products one of the most common sources of carotenoids available for the human population.

Tomatoes and tomato-based foods account for over 85% of all the dietary sources of lycopene [22]. Lycopene is the most abundant carotenoid in ripe tomatoes, representing about 80 to 90% of these pigments [23]. Normally, tomatoes contain up to 10 mg lycopene per 100 g of fresh weight [3], depending on some factors such as those mentioned above. Additionally, the lycopene content increase as the fruit ripens [24]. Chemically, lycopene (Fig. **1**) is a polyunsaturated (polyene) straight-chain molecule with 11 conjugated and 2 nonconjugated double bonds. Thus, it can be found in both the *cis* and *trans* configurations because of the presence of the double bonds [25]. Additionally, its straight structure facilitates its incorporation into some organs such as the liver, adrenal glands and prostate, where it has a role of preventing oxidative reactions associated with the outbreak of different diseases [26]. The *trans* configuration is the most common isomer and largely responsible for the deep red colour of the ripe red tomatoes [25, 27]. Nevertheless, the *trans* form is prone to isomerisation under the influence of some processing conditions, which include the action of light, heat, oxygen and acids, and, after ingestion, it is partly transformed *in vivo* to the more bioactive *cis* form [14, 28]. Lycopene has strong antioxidant activity and other *in vitro* and *in vivo* beneficial effects because of its capacity to act as a free radical scavenger [29] that is twice that of β-carotene (Fig. **2**) [22]. In ripe red tomato fruits, the ratio of lycopene to β-carotene content varies widely between 1.5 and 40 [30, 31]. Along with α-carotene and β-cryptoxanthin, β-carotene is a provitamin A carotenoid, *i.e.*, it can be converted by the human body into two molecules of vitamin A (Fig. **2**). Actually, what we generally call vitamin A is a group of naturally-occurring molecules, structurally similar to retinol, that are capable of exerting biological activity [32]. In addition to lycopene and β-carotene, phytoene, phytofluene, ζ-carotene, γ-carotene, neurosporene and lutein are other carotenoids reported in tomatoes and tomato-based products [33].

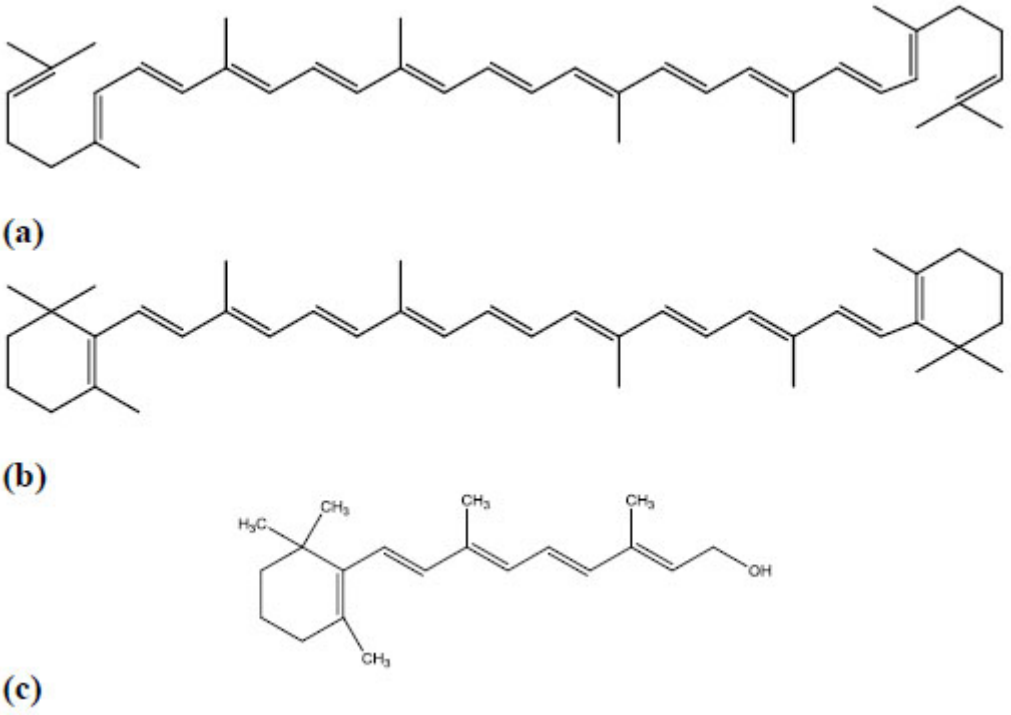


**Fig. (2).** Chemical structures of **(a)** lycopene, **(b)** β-carotene and **(c)** vitamin A.

## Vitamins

Vitamin C and E are the respective generic names for ascorbic acid and tocopherols. Ascorbic acid, a 6-carbon lactone ring structure with a 2,3-enediol moiety, can be found in all living and actively metabolising plant parts and cell compartments [34]. It comprises two compounds endowed with bioactivity: $_{L}$-ascorbic acid and $_{L}$-dehydroascorbic acid (Fig. **3**). Both are easily absorbed by the gastrointestinal tract and can interchange enzymatically *in vivo*. In biological systems, ascorbic acid exists as the monovalent anion $_{L}$-ascorbate [35]. However, this vitamin is highly susceptible to oxidation in the presence of metal ions like $Cu^{2+}$ and $Fe^{3+}$. Its oxidation is also influenced by light, heat, pH, oxygen and water activity [36]. This vitamin has the ability to act as electron donor, being a potent *in vivo* antioxidant; it protects low-density lipoproteins (LDL) from the oxidation caused by different oxidative stress reactions and inhibits the LDL oxidation caused by vascular endothelial cells. The high volume of consumption of tomato all the year round makes this fruit one of the main sources for this vitamin.

Different levels of ascorbic acid have been reported in tomatoes (8-21 mg/100 g of fresh weight) [4, 37, 38], since it is affected by different factors. In turn, vitamin E includes eight chemically distinct molecules (Fig. **4**), four tocopherol isoforms (α-, β-, γ- and δ-tocopherol) and four tocotrienol isoforms (α-, β-, δ- and γ-tocotrienol) [39]. Tocopherols differ from the corresponding tocotrienols in the aliphatic tail; tocopherols have a phytyl side chain attached to the chromanol head, whereas the tail of tocotrienols contains three *trans* double bonds at the 3', 7' and 11' positions and forms an isoprenoid chain. These unsaturations in the tail of tocotrienols give only a single stereoisomeric carbon, whereas tocopherols have eight possible stereoisomers per structural formula. The various isoforms differ in the methyl substituents on the chromanol head; the α-forms contain three methyl groups, the β- and γ- have two and the δ-forms have only one methyl group. Together, tocopherols and tocotrienols are called tocochromanols. All these compounds feature a chromanol ring with a hydroxyl group capable of donating a hydrogen atom, and a lipophilic side chain that allows for penetration into cell membranes [34]. The donation of hydrogen atoms to the peroxyl radicals forms unreactive tocopheroxyl radicals (TO˙) unable to continue the oxidative chain reaction [40]. The human body absorbs all forms of vitamin E, but maintains only the α-tocopherol [41]. The amounts of tocopherols also vary in tomatoes, having been reported values from 0.17 to 1.44 mg/100 g of fresh weight [4, 38]. Nevertheless, neither vitamin C nor vitamin E can be synthesized by humans, so their intake must be guarantee through the diet [34, 42].

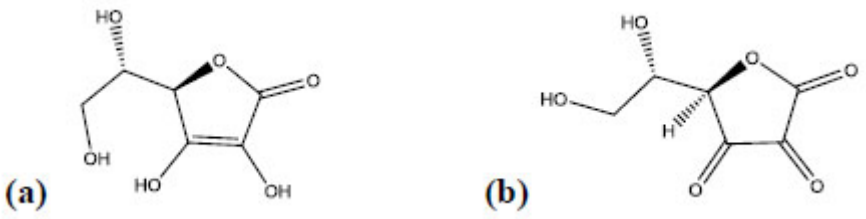


**Fig. (3).** Chemical structures of **(a)**$_L$-ascorbic acid and **(b)**$_L$-dehydroascorbic acid.

The tomato fruit also presents folates (12-18 µg/100 g of fresh weight) [43, 44], a complex group of water-soluble compounds known as vitamin $B_9$. Folic acid (Fig. **5**) consists in an aromatic pteridine ring attached by a methylene bridge to a residue of *p*-aminobenzoic acid which, in turn, is joined by an amide bond to a

glutamic acid residue [45]. Folate vitamers are involved in multiple physiological mechanisms in the field of andrology and gynecology [46] and are essential for fetal growth [47]. Folates also are involved in the homocysteine metabolism regulation [48] and some authors consider the hyperhomocysteinemia condition as a marker or risk factor for cardiovascular diseases [49, 50]. As folates are synthesised just by plants and microorganisms, humans are dependent on dietary sources like the tomato fruit for the intake of this vitamin.

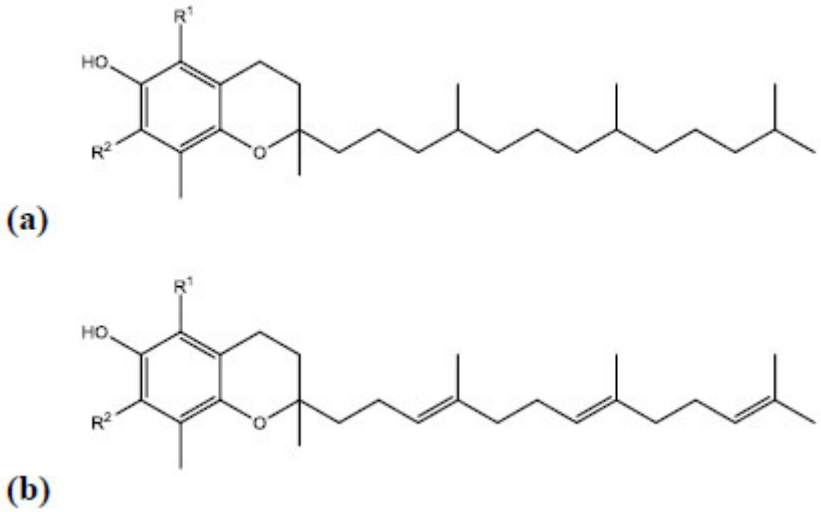


**Fig. (4).** Chemical structures of **(a)** tocopherols ($R^1 = R^2 = Me$: α-tocopherol; $R^1 = Me$, $R^2 = H$: β-tocopherol; $R^1 = H$, $R^2 = Me$: γ-tocopherol; $R^1 = R^2 = H$: δ-tocopherol) and **(b)** tocotrienols ($R^1 = R^2 = Me$: α-tocotrienol; $R^1 = Me$, $R^2 = H$: β-tocotrienol; $R^1 = H$, $R^2 = Me$: γ-tocotrienol; $R^1 = R^2 = H$: δ-tocotrienol).

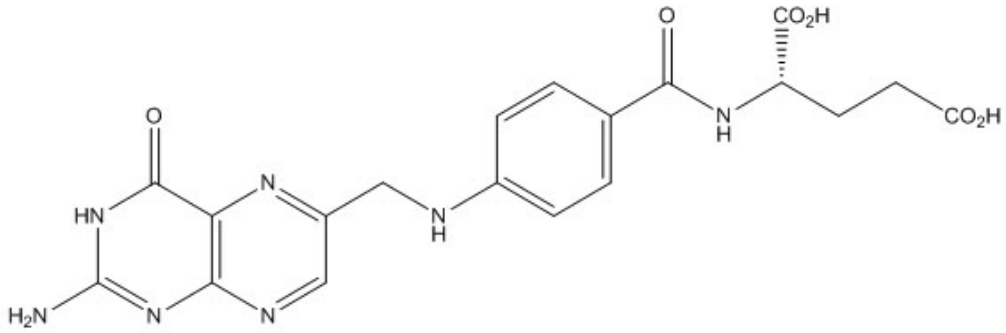


**Fig. (5).** Chemical structure of folic acid.

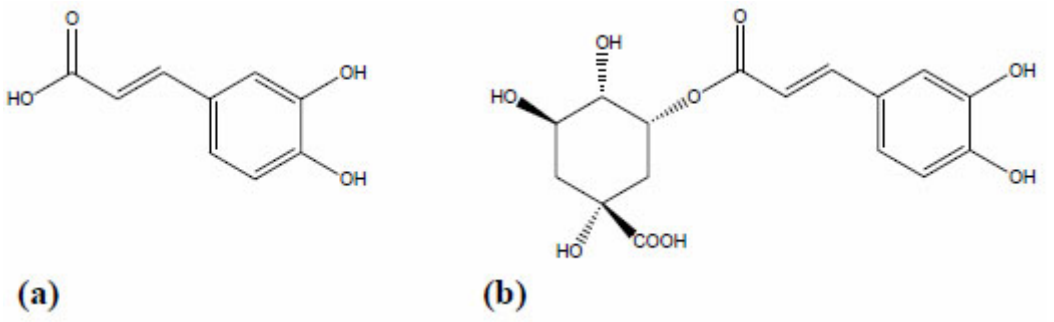


**Fig. (6).** Chemical structures of **(a)** caffeic acid and **(b)** chlorogenic acid.

## Phenolic Compounds

Phenolic compounds are broadly spread throughout the plant kingdom, representing more than 8000 different phenolic structures. They have at least one aromatic ring with one or more hydroxyl groups attached and vary from low molecular weight molecules to large and complex ones. Phenolic compounds generally appear as esters and glycosides rather than as free compounds due to the conferred stability of these molecules. Phenolic (hydroxycinnamic) acids and flavonoids are the most abundant phenolic compounds in tomatoes [5], as well as in the diet [51]. The phenolic acids represent a group of compounds that derive from cinnamic acid through the phenilpropanoid pathway. They display a $C_6$-$C_3$ skeleton of *trans*-phenyl-3-propenoic acid with one or more hydroxyl groups bonded to the phenyl moiety, some of which may be methylated. According to literature, caffeic acid and its ester chlorogenic acid are the main phenolic acids in tomato (Fig. **6**) and the most extensively studied [5, 52]. Both compounds have *in vitro* antioxidant activity [53] and might inhibit the formation of mutagenic and carcinogenic *N*-nitroso compounds [54]. Curiously, the antioxidant mechanism of chlorogenic acid is analogous to that of lycopene. The flavonoids are the largest group of molecules within the phenolic compounds. These polyphenolic compounds display an arrangement of three aromatic rings with 15 carbons and a $C_6$-$C_3$-$C_6$ skeleton which can have numerous substituents. The A ring is a benzene, condensed with a six-member ring (ring C), which carries a phenyl benzene in position 2 (ring B) as a substituent. Sugars in the form of glycosides are normally joined with flavonoids and while they increase water solubility along with hydroxyl groups, other substituents like methyl groups and

isopentenyl units increase their lipophilic properties [39]. In tomatoes, flavonoids are represented by flavanones, including naringenin glycosylated derivatives, and flavonols such as quercetin, rutin and kaempferol glycosylated derivatives (Fig. **7**) [55 - 58]. They are commonly found in the skin and in small amount in the other parts of the fruit.

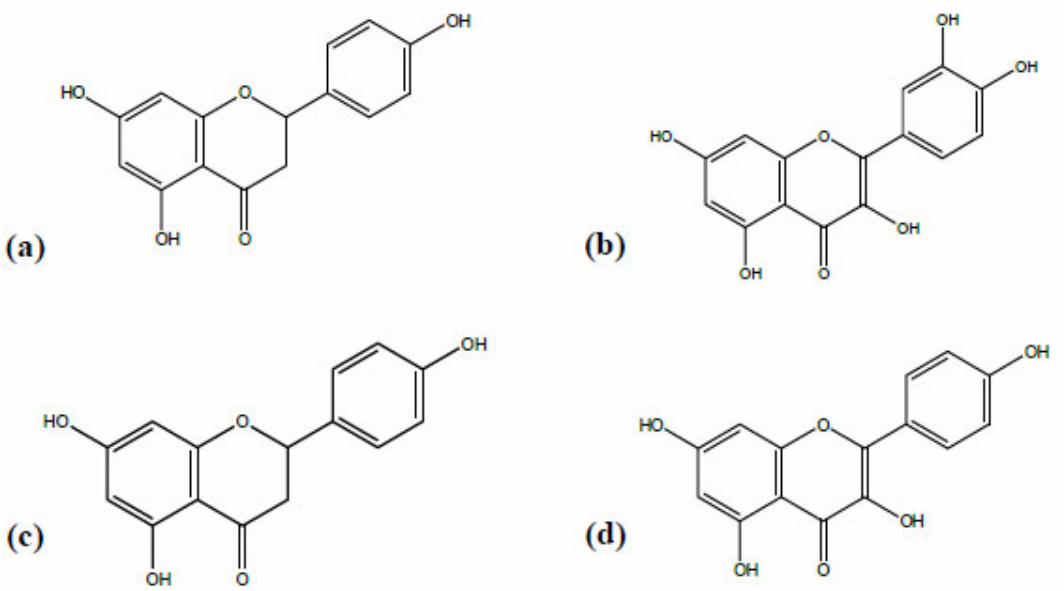


**Fig. (7).** Chemical structures of **(a)** naringenin, **(b)** quercetin, **(c)** rutin and **(d)** kaempferol.

## Glycoalkaloids

Glycoalkaloids are characteristic secondary metabolites in plants of the Solanaceae family. They are involved in host-plant resistance and have pharmacological and nutritional effects in humans and animals. In tomato plants, the glycoalkaloids tomatine and esculeoside A (Fig. **8**) are synthesized. Tomatine comprises a junction of α-tomatine and dehydrotomatine (Fig. **8**). Structurally, dehydrotomatine differs from α-tomatine by having a double bond in the steroidal ring B of the aglycone. However, both glycoalkaloids have the same tetra-saccharide (lycotetraose) side chain; α-tomatine has lycotetraose bonded to the aglycone tomatidine, whereas dehydrotomatine has the side chain attached to an aglycone tomatidenol [14, 15]. Unripe tomatoes may contain up to 500 mg of tomatine per kg of fresh weight; but the levels are decreased with the ripening of

tomatoes and, therefore, ripe red tomatoes present lower levels (~5 mg/kg of fresh weight) [59]. Beside, the tomatine content of cherry tomatoes is several fold greater than that of larger size standard varieties. On the other hand, the content of esculeoside A, which is stored in ripe fruits of cultivated tomatoes, is comparable to or higher than that of lycopene [60, 61]. Thus, the levels of esculeoside A increase as the fruit matures, contrary to that observed for tomatine [14, 62].

## BIOAVAILABILITY OF TOMATO COMPOUNDS

The bioavailability of bioactive compounds is crucial to their physiologic effect. Before becoming bioavailable, the tomato bioactive compounds must be released from the plant matrix and modified in the gastrointestinal tract. The digestive transformations that involve the conversions of tomato into substances ready to be absorbed and assimilated are called bioaccessibility. It is commonly assessed using *in vitro* digestion assays, which simulate the gastric and small intestinal digestion processes. Differently, the term bioavailability can be defined as the fraction of a compound or metabolite that reaches the systemic circulation. It is evaluated using *in vivo* assays in animals or humans by measuring the concentration of a compound in plasma or urine after administration of an acute or chronic dose of the isolated compound or compound-containing food [63].

### Bioavailability of Carotenoids

The bioavailability of the tomato carotenoids is widely affected by endogenous (tomato-related) and exogenous (processing-related) factors. Firstly, in order to become bioaccessible, carotenoids need to be released from the tomato matrix in which they are embedded. Thereafter, they need to solubilise into an oil phase either during processing and/or during the gastric digestion. The release of carotenoids from the tomato matrix and its subsequent incorporation in the oil and micellar phase are decisive steps during digestion in order to become bioavailable.

In fact, the mixed micelles formed in the small intestine are the primary vehicle for the absorption of carotenoids *via* intestinal mucosa [64]. That's why the bioavailability is greatly affected by dietary composition, *i.e.*, the co-ingestion of carotenoids and fat is very important and necessary for absorption [65 - 67]. Actually, the Mediterranean way of preparing tomatoes, by cooking them in olive

oil, is a smart way to promote the absorption of these bioactive compounds. Regarding exogenous factors, it is know that the lycopene bioaccessibility increases under processing conditions because cell membranes are disrupted, which increases its release from the tomato matrix [21]. Thermal treatments also promote the lycopene isomerisation of *trans* to *cis* form, isomer that is described as being more bioavailable [28, 68]. Thus, lycopene from tomato-based processed foods is generally more bioavailable than from fresh tomatoes. Nevertheless, inadequate processing and storage conditions can cause isomerisation during the formation of by-products, which can reduce the absorption of carotenoids and make the food less desirable to the consumer.

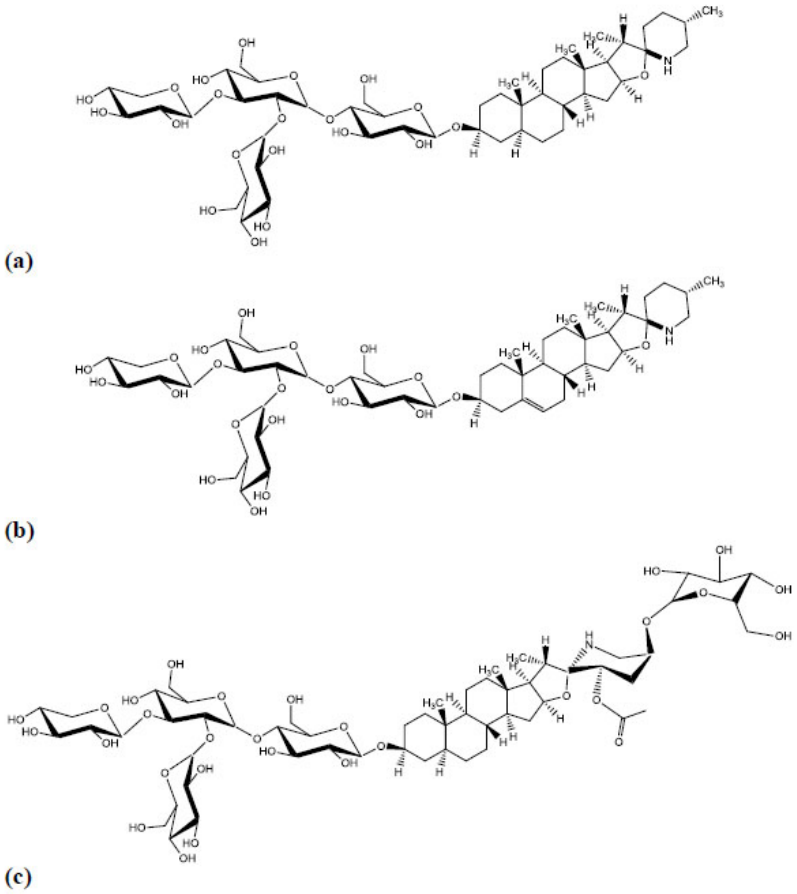


**Fig. (8).** Chemical structures of **(a)** α-tomatine, **(b)** dehydrotomatine and **(c)** esculeoside A.

## Bioavailability of Vitamins

The ingestion of ascorbic acid causes a dose-dependent increase of this vitamin in the plasma. Its absorption from the gastrointestinal tract occurs by a sodium-dependent active transport mechanism (mainly in the jejunum) but also by a passive absorptive pathway. The active transport predominates when ascorbic acid is at low gastrointestinal concentrations, but when at high concentrations the active transport becomes saturated allowing only passive diffusion [35]. In turn, the absorption of tocopherols is similar to that observed for other fat-soluble vitamins, being necessary it's packaging into micelles (emulsified in the presence of bile salts and amphipathic lipids available in the intestinal lumen) to facilitate their absorption during digestion, the same as carotenoids. After entry into the intestinal absorptive cells (enterocytes), tocopherols are packaged into chylomicrons and enter the circulation through the lymph-vascular system. Thereafter, chylomicrons triglycerides are hydrolyzed by endothelial bound lipoprotein lipases, resulting in the transfer of tocopherols and lipids to peripheral tissues [69]. However, the main steps and molecular mediators of the tocopherols transport from the luminal micellar phase into the enterocytes are not yet fully elucidated.

## Bioavailability of Phenolic Compounds

The bioavailability within the class of phenolic compounds is widely variable and the most abundant in our diet do not always correspond to those with better bioavailability. The ability of the human body to absorb and metabolize these compounds varies widely depending primarily on their physicochemical properties, such as the basic structure, molecular size, degree of polymerization or glycosylation, solubility and conjugation with other phenolics [63]. Phenolic acids of low-molecular weight such as gallic acid are easily absorbed by the small intestine, as well as flavones and quercetin glycosides [70]. Conversely, larger polyphenols are poorly absorbed. In addition, a large number of phenolic compounds is found in the glycosylated form or as esters or polymers which must be hydrolyzed before the free aglycone can be absorbed. The human metabolism also greatly affects the bioavailability of these bioactive compounds. Once absorbed, polyphenols undergo biotransformations in the small intestine, and later

in the liver, into various *O*-sulfated, *O*-glucuronidated and *O*-methylated forms. Thus, the chemical structure of the resultant metabolites could be quite different from that of the parent compounds and, therefore, these metabolites may or not have the initial biological activity [71]. Moreover, the bioavailability of the phenolic compounds can be influenced by different food processing steps. For example, it has been demonstrated a significant increase in the levels of chlorogenic acid and naringenin in plasma after consumption of cooked tomatoes in comparison with fresh tomatoes [72]. Actually, mechanical and thermal treatments involved in the manufacture of tomato sauce helps to release these bioactive compounds from the tomato matrix, thus increasing the bioavailability more efficiently than through the addition of oil [73].

### Bioavailability of Glycoalkaloids

Very limited studies have been conducted to study the bioavailability of glycoalkaloids in humans, but it is known that these compounds are poorly absorbed by the gastrointestinal tract of mammals. An appreciable amount of the ingested glycoalkaloids is hydrolyzed in the gut to less toxic aglycones, and the originated metabolites are rapidly excreted *via* urine and feces [74].

## BIOACTIVITY OF TOMATO COMPOUNDS

Bioactivity can be defined as the effect caused upon exposure to an active ingredient. It comprises tissue uptake, as previously referred, and the resulting physiological response, which can be evaluated *in vivo*, *ex vivo* or using *in vitro* assays. The tomato compounds are known for their capacity to act as free radical scavengers of reactive oxygen and nitrogen species (ROS/RNS). These species include free radicals and other non-radical reactive substances also called oxidants. ROS and RNS are generated as a normal part of human metabolism and its production can be promoted by external factors. The accumulation of these species in the body gives rise to a phenomenon known as oxidative stress, which results from an imbalance between generation and neutralization of reactive species in the cells. The main targets of these species are proteins, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) molecules, lipids and sugars. The lipid peroxidation is one of the most undesirable effects of ROS

because of the consequent formation of free radicals. This phenomenon is initiated by an attack towards a fatty acid side chain by a radical in order to abstract a hydrogen atom. A higher number of double bonds in the fatty acid facilitate the removal of hydrogen atoms and consequently the formation of radicals. After that, the carbon-centred lipid radical can undergo molecular rearrangement and react with oxygen forming a peroxyl radical. These highly reactive species can abstract hydrogen atoms from surrounding molecules and propagate the lipid peroxidation chain reaction. Hydroxyl radicals are major radicals in lipid peroxidation mechanisms [39, 75]. Products generated by these chain reactions are toxic, *e.g.*, malondialdehyde (MDA) may be involved in the onset of mutagenic damage. ROS can also activate the transcription nuclear factor kappa B (NF-κB), which leads to the expression of pro- and anti-inflammatory cytokines genes and their subsequent production [76]. As a consequence, these processes play a key role in the development of several degenerative and chronic diseases, as well in aging. The main mechanisms and properties inherent to the bioactivity and protective effects of the major tomato compounds are discussed below.

## Bioactive Properties of Carotenoids

Carotenoids can inhibit the lipid peroxidation due to their capacity to act as free radical scavengers [29]. The basic antioxidant properties of these pigments are conferred by its singlet oxygen quenching capacity, by which the carotenoids are excited. The excited carotenoids can dissipate the excess energy through a sequence of rotational and vibracional interactions that allows them to return to the unexcited state, and so quench more radicals. Indeed, these bioactive compounds are known for its capacity to scavenge peroxyl radicals more efficiently as compared to others ROS [77]; however, these radicals are the only ones able to annihilate these pigments [39]. Carotenoids may also decay and form non-radical compounds able to stop free radical attacks through its binding to these radical species [39, 78]. Nevertheless, its effects in humans are quite complex and it is still unclear whether these biological effects result from their antioxidant capacity or of a non-antioxidant mechanism [34]. According to Navarro-González *et al.* [27], the mechanism of action of lycopene include: its role as an antioxidant, decreasing the LDL oxidation and the lipid peroxidation and lowering the LDL cholesterol and the total cholesterol, and as a modulator of

inflammatory response through the reduction of cytokines implicated in cardiovascular disease. Lycopene has also influence on cellular proliferation and differentiation as well as in the immune response [79]. Curiously, lycopene has the capacity to inhibit the lipopolysaccharide-induced phenotypic and functional maturation of murine dendritic cells both *in vitro* and *in vivo* [80]. It also reduces the oxidative stress and intestinal inflammation in experimental models of colitis in rats [81]. As mentioned above, the high number of conjugated double bonds in lycopene structure provides the singlet oxygen quenching capacity. Lycopene and β-carotene reduce the production of LDL cholesterol oxidized products that are associated with coronary heart disease; β-carotene also protects the skin against deleterious effects of sunlight [77]. The antioxidant potential of carotenoids is commonly linked to its capacity to prevent free radical triggered diseases, including atherosclerosis, multiple sclerosis, age-related muscular degeneration and cataracts [36]. In fact, the consumption of tomatoes and tomato-based foods has been significantly connected to a low incidence of prostate cancer [82].

## Bioactive Properties of Vitamins

The antioxidant activity of tocopherols is conferred by the chromanol head group. The phytyl side chain has no activity; it is embedded within the cell membrane bilayer while the active chromanol ring is closely positioned to the surface. This ingenious arrangement allows tocopherols to act as powerful antioxidants and to be regenerated through reaction with other antioxidants, *e.g.*, ascorbic acid [36]. However, the activity of these antioxidants is affected by its orientation within the membrane. Thus, the tocopherols halts lipid peroxidation in cell membranes and various lipid particles through donation of the phenolic hydrogen of the chromanol ring to lipid peroxyl radicals, thereby forming unreactive tocopheroxyl radicals unable to continue the oxidative chain reaction [83]. This vitamin protects LDL and cell membrane polyunsaturated fatty acids, and inhibits smooth muscle cell proliferation and protein kinase C activity [36]. Curiously, tocopherols are the major lipid-soluble antioxidants found in plasma, red cells and tissues [40]. They have been associated with lower incidence of heart disease, delay of Alzheimer's disease, and prevention of several types of cancer. The α-tocopherol, for example, can reduce the nitrogen dioxide levels more effectively than the other isoforms, a compound implicated in arthritis and carcinogenic processes [36]. However,

tocopherols are not efficient scavengers of hydroxyl radicals *in vivo* [84].

The bioactivity of ascorbic acid is conferred by the 2,3-enediol. The antioxidant mechanisms are conferred by its ability to donate a hydrogen atom to free radicals, to eliminate molecular oxygen and quench singlet oxygen. The capacity to scavenge aqueous radicals and regenerate α-tocopherol from tocopheroxyl radicals are other well-known antioxidant mechanisms of this vitamin [36, 84]. In biological systems, ascorbic acid changes to the ascorbate radical through the donation of an electron to a lipid radical in order to stop the lipid peroxidation chain reaction. Thereafter, the originated ascorbate radicals react rapidly and produce one molecule of ascorbate and other of dehydroascorbate. The last one is devoid of bioactivity, but is converted back into ascorbate [77]. Ascorbic acid is efficient in scavenging the superoxide radical anion, hydroxyl radicals, singlet oxygen, hydrogen peroxide and reactive nitrogen oxide. However, the ascorbic acid may also act as a prooxidant, for example during the reduction of ferric iron ($Fe^{3+}$) to the more active ferrous iron ($Fe^{2+}$) [36].

The vitamin A has high antioxidant activity and can protect lipids against rancidity. In humans, it plays a vital role in protecting LDL from oxidation stimulated by copper [85]. Retinoids are essential to diverse physiological functions including vision, immune response, bone mineralization, reproduction, cell differentiation, and growth [32].

## Bioactive Properties of Phenolic Compounds

The antioxidant capacity of phenolic acids comes from its ability to chelate transition metals and to scavenge free radicals, having a significant impact over hydroxyl and peroxyl radicals, peroxynitrites and superoxide anions [39]. The hydroxycinnamic acid derivatives display bioactivity due to the hydroxylation and methylation patterns of the aromatic ring, *e.g.*, the *o*-dihydroxy group in the phenolic ring of caffeic acid improves its antioxidant capacity [86]. The free radical scavenging mechanism of the hydroxycinnamic acids is analogous to that of flavanoids, which is attributed to its capacity to donate a hydroxyl hydrogen and resonance stabilization of the resulting radicals. The *o*-dihydroxy substituents also have iron-chelating ability [77].

The bioactivity of flavonoids is conferred by hydroxyl groups attached to the ring structures. They can act as reducing agents, hydrogen donators, superoxide radical scavengers, singlet oxygen quenchers, and metal chelators. Flavonoids have capacity to protect the DNA from damage caused by hydroxyl radicals, reduce tocopheroxyl radicals, activate or inhibit bioactive enzymes, and alleviate the nitrosative stress [39, 77, 87]. Rutin, also known as vitamin P, has antioxidant, anti-inflammatory, and anticarcinogenic properties. It reduces the fragility of blood vessels [88]. At a low concentration of cupric ions, quercetin is capable of protecting DNA from oxidative damage resulting from the attack of the hydroxyl and superoxide radicals and hydrogen peroxide [77].

## Bioactive Properties of Glycoalkaloids

Glycoalkaloids are perceived as potentially toxic, but the studies conducted over the past decade indicate that they may also have health-promoting effects, depending on dose and conditions of use. They can be used because of its anti-inflammatory, anticancer, antipyretic, anticholesterol, antinociceptive, and anti-microbial effects [89]. Its bioactivity derives mainly from the capacity to inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), and from its ability to complex with membrane 3$\beta$-hydroxy sterols, which causes the rupture of the membrane. Its capacity to inhibit AChE and BuChE makes them important compounds, but the source of enzymes to be tested (plasma *vs*. serum) and differences in the purity of the glycoalkaloid and aglycones have affected the published results [89, 90]. However, the aglycone alone is practically inactive against the cholinesterase enzymes. The sugar unit is required for activity, but it is the structure of the aglycone which determines the extent of inhibition. The existence of heterocyclic nitrogen is also a necessary condition for activity [91]. Regarding the second mechanism of action, and with respect to the aglycone subunit, an intact E ring and an unshared pair of electrons on the nitrogen of the F ring, as well as solanidane and spirosalane rings are necessary for membrane lytic activity [92]. In general, the glycoalkaloids bioactivity increases when they are administered as mixtures (depending on the relative proportion used) [89]. However, the synergistic activity of α-tomatine and dehydrotomatine remains unknown. In inflammatory processes, the aglycone tomatidine has the capacity to reduce inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2)

expression through blocking NF-κB and JNK signalling in lipopolysaccharide-stimulated macrophages [93]. In turn, α-tomatine has the ability to decrease the cholesterol and triglycerols levels, enhance the immune system, and inhibit the growth of cancer cells [94 - 96]. Actually, this compound has been recognized as a potential anticancer drug [97]. Nevertheless, a deeper understanding of the implications of glycoalkaloids in the human diet is still necessary.

## TOMATO AND HUMAN HEALTH

The regular consumption of tomatoes and tomato-based foods has been associated with several positive effects on human health. Current studies demonstrate the several benefits of tomato bioactive compounds, either isolated or in combined extracts, namely anticarcinogenic [9, 82], cardioprotective [8, 12, 98], anticholesterolemic [99, 100], antidiabetic [101], and hepatoprotective [102, 103] effects among other health benefits, mainly due to its antioxidant [4, 8, 104] and anti-inflammatory [7, 104] properties. Indeed, the production of ROS and RNS during oxidative stress and inflammatory processes is widely associated with the development and progression of chronic diseases such as cancers, cardiovascular diseases, diabetes, and other disorders associated with aging [105, 106]. The tomato bioactive compounds can neutralize the generated reactive species and, therefore, prevent the associated diseases. In fact, low levels of antioxidants have been associated with heart diseases and different types of cancer [107]. Examples of *in vitro* and *in vivo* clinical trials highlighting the crucial role of tomato and tomato-derived compounds on human health are presented below.

### Tomato Consumption Improves the Oxidative Status

The involvement of oxidative stress in the pathogenesis of various degenerative diseases is evidenced by an altered expression of enzymatic antioxidant defences, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) [108]. A recent study conducted by Li *et al.* [104] demonstrated that the anti-inflammatory effect of the purple tomato extract might be caused by the decreased levels of MDA and nitric oxide (NO) and increased GPx and SOD activity in oedematous tissue. These results were attributed to the direct antioxidant activities of the bioactive compounds towards the free radicals, and

indirect elevation of the enzyme activity. Supplementation of ultra marathon runners for a period of two months with a whey protein bar and tomato juice also improved the oxidative status, decreasing thiobarbituric acid reactive substances (TBARS) and protein carbonyls [8]. Other study evaluated the effect of tomato sauces with different amounts of lycopene on oxidative stress biomarkers [109]. Healthy participants consumed 160 g/day of tomato sauce, while maintaining constant their usual diet and physical activity. The regular consumption of the lycopene-enriched tomato sauce caused a considerable decrease of the oxidized-LDL cholesterol levels and increased the total plasma antioxidant capacity. Thus, the putative role of lycopene in combination with other tomato bioactive ingredients in the prevention of oxidative stress related diseases was evidenced.

**Tomato Suppresses the NF-κB Activation and Reduces Inflammation**

Inflammation is a normal protective response of the innate immune system to an injury. However, when the oxidative damage is out of control, inflammation may become chronic leading to tissue damage. During inflammation, immune cells are activated and release increased levels of ROS to eliminate invading pathogens. The intracellular ROS production is linked to various cellular processes controlled by NF-κB (which is the central orchestrator of the inflammatory response), including activation of NAD(P)H oxidase, matrix metalloproteinases (MMP-1, MMP-2 and MMP-9), nitric oxide synthases (NOS), xanthine oxidase, cyclooxygenase-2 (COX-2), and lipooxygenases. Additionally, immune cells release a number of proinflammatory mediators such as cytokines (tumour necrosis factors (TNF-α) and interleukin (IL-6, IL-1β), chemokines (IL-8), cell adhesion molecules (CAMs), C-type lectin receptors, prostaglandins, leukotrienes, and NO [110, 111].

Clinical trials demonstrated that the anti-inflammatory effects of tomato compounds are attributed to their capacity to suppress of the activation of NF-κB. De Stefano *et al.* [112] investigated the effect of PS (a polysaccharide from unripe tomato peels) on nitrite and ROS production in J774 macrophages stimulated by bacterial lipopolysaccharide (LPS) for one day. Results demonstrated that PS inhibits NF-κB activation and inducible nitric oxide synthase (iNOS) gene expression by preventing the reactive species production; thus, the involvement of

this compound in the control of the oxidative stress and/or inflammation was suggested. Joo *et al.* [113] studied the effects of a tomato lycopene extract on the LPS-induced innate signalling and on the acute and spontaneous chronic intestinal inflammation. Mice were fed a diet containing 0.5 and 2% tomato lycopene extract or an isoflavone free control. The tomato lycopene extract prevented LPS-induced proinflammatory gene expression by blocking of NF-κB signalling, through aggravation of dextran sulfate sodium-induced colitis by enhancing epithelial cell apoptosis. The effectiveness of the combination of carotenoids and phenolics in inhibiting the release of inflammatory mediators from macrophages exposed to LPS and the anti-inflammatory effect in an *in vivo* mouse model of peritonitis was evaluated by Hadad & Levy [7]. Pre-incubation of macrophages with the evaluated compounds, 1 h before the addition of LPS for one day, caused a synergistic inhibition of NO, prostaglandin E(2), and superoxide anion production derived from down-regulation of iNOS, COX-2, and NADPH oxidase protein and mRNA expression and synergistic inhibition of TNF-α secretion. The supplementation of mouse resulted in attenuated neutrophil recruitment to the peritoneal cavity and inhibited inflammatory mediator production by peritoneal neutrophils and macrophages.

**Tomato Reduces Inflammation Linked to Obesity, Diabetes and Cholesterol**

Obesity is a chronic inflammatory state in which the augmented level of body fat leads to an increase in circulating inflammatory mediators [101]. Ghavipour *et al.* [101] demonstrated that tomato juice reduces inflammation in overweight and obese females. In this study, inflammatory biomarkers were analyzed in an intervention group that consumed 330 mL/day of tomato juice for 20 days. Serum levels of IL-8 and TNF-α decreased considerably in the intervention group compared with the control one. Curiously, this effect was confined to overweight subjects. Among obese subjects, the levels of serum IL-6 were reduced in the intervention group, while the levels of IL-8 and TNF-α showed no difference from the control group. Thus, the authors concluded that increased tomato intake may reduce the risk of inflammatory diseases associated with obesity such as cardiovascular disease and diabetes. Another study showed beneficial effects of tomato juice consumption on oxidative stress status of overweight females [11]. Some evidence suggests that oxidative stress, in addition to being a consequence

of fat accumulation with subsequent inflammatory response, may be a prerequisite for adipogenesis [114]. The authors verified that the plasma total antioxidant capacity and erythrocyte antioxidant enzymes increased and serum MDA decreased after the 20 days of intervention period. Thus, it was concluded that the verified reduction of oxidative stress in weight females may prevent from obesity related diseases and promote health.

The supplementation effect of tomato juice on indices associated with metabolic health and adipokine profiles in young healthy women, to which was given 280 mL of tomato juice (containing 32.5 mg of lycopene) daily for 2 months, was studied by Li *et al.* [10]. It was found that the tomato juice supplementation significantly reduced the body weight, body fat, body mass index, waist circumference, and the serum levels of cholesterol and TBARS; while the serum levels of adiponectin, triglyceride, and lycopene were significantly increased. Other authors evaluated the effect of pre-meal tomato intake in the anthropometric indices and blood levels of triglycerides, cholesterol, glucose, and uric acid in an intervention group consisting of young adult women [100]. The intervention group ingested a raw ripe tomato (~90 g) before lunch for 4 weeks. At the end of that period, it was observed a positive effect in body weight, fat percentage, and blood levels of glucose, triglycerides, cholesterol, and uric acid of the participants.

Regarding studies in animal models, Seo *et al.* [115] investigated the anti-obesity properties of a tomato vinegar beverage in diet induced obese C57BL/6 mice. The prepared beverage not only reduced fat accumulation, but also insulin resistance; these changes were mediated by the AMP-activated protein kinase and peroxisome proliferator-activated receptor alpha up-regulation. In a similar study conducted by Choi *et al.* [99] it was concluded that green tomato extracts attenuate high-fat diet-induced obesity in C57BL/6 mice through activation of the adenosine monophosphate-activated protein kinase (AMPK) pathway, and that green tomato extracts may be a potential candidate for anti-obesity drugs. Besides, the results indicated that tomatine may be responsible for the observed reduction of body weight. It has been reported that the glycoalkaloid tomatine forms insoluble complexes with cholesterol *in vitro*. In this sense, to evaluate the capacity of tomatine in reducing dietary cholesterol absorption and the plasma levels of cholesterol and triglycerides, hamsters were fed a high-fat, high-

cholesterol diet containing 0.05-0.2% of tomatine [116]. The tomatine diet decreased the serum LDL levels without changing HDL cholesterol, being more cholesterol and coprostanol excreted in feces corresponding to the ingested quantity of tomatine. Moreover, these findings suggest that due to the formation and excretion of tomatine-cholesterol complexes, just a very small amount of dietary tomatine is absorbed by the human body.

## Tomato Prevents Cardiovascular Diseases, Atherosclerosis and Hypertension

Currently, cardiovascular disease still represents a major cause of morbidity and death in the world [117]. The endothelium plays a crucial role in cardiovascular health; its dysfunction is associated with the development of atherosclerosis, hypertension and heart failure. Endothelial cells respond to different stimuli through the synthesis and release of several molecules capable of regulating vascular tone, permeability, and inflammation, as well as the blood fluidity and coagulation [118]. Indeed, endothelial dysfunction is a key early step in the development of cardiovascular diseases. It is characterized by an impairment of endothelium-dependent relaxation and a predisposition to a proinflammatory and prothrombotic state [119, 120]. NO contributes to the maintenance of vascular integrity thanks to its antithrombotic, antiatherogenic, and antiproliferative properties. For this reason, decreased levels of NO have been linked with various cardiovascular disorders including hypertension, atherosclerosis and ischaemic disease. The tomato bioactive compounds could contribute to cardiovascular health, and its benefits have been reported in several *in vitro* and *in vivo* studies.

Regarding *in vivo* studies, Kim *et al.* [121] demonstrated that elevated levels of serum lycopene reduce the oxidative stress correlated to endothelial function. Clinical trials were conducted in healthy men who received 15 mg/day of lycopene for 8 weeks. After treatment, serum lycopene levels increased in a dose-dependent manner. The group who received lycopene showed a greater increase in plasma SOD activity and reduction in lymphocyte DNA comet tail length, as well as an increase in reactive hyperemia peripheral arterial tonometry (RH-PAT) index. Moreover, high-sensitivity CRP (hs-CRP), systolic blood pressure, soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) were significantly decreased, and β-carotene and LDL-

particle size were increased. A remarkable beneficial effect of lycopene supplementation on the endothelial function (*i.e.*, RH-PAT and sVCAM-1) in subjects with an initially relatively impaired endothelial cell function was also observed. Another study showed that the vascular endothelial function of ultra marathon runners is improved by its supplementation with tomato juice for a period of 2 months [8].

The suitability of tomato paste (a concentrated of bioactive compounds) for modifying postprandial oxidative stress, inflammation, and endothelial function in healthy weight individuals was evaluated by Burton-Freeman *et al.* [122]. Participants consumed high-fat meals on two separate occasions containing a processed tomato product or a placebo. Both meals increased the plasma levels of glucose, insulin and lipids. Tomato significantly attenuated the high-fat meal-induced LDL oxidation and the increase in interleukin-6 (IL-6), a proin-flammatory cytokine and inflammation marker. Thus, it was demonstrated that the inclusion of tomatoes or tomato-based foods at the meal reduces the postprandial lipemia-induced oxidative stress and the associated inflammatory response. Furthermore, these findings highlighted the potential protective role of tomato fruit in reducing the risk of cardiovascular disease. Beneficial effects of daily tomato paste consumption on endothelial function were also demonstrated by Xaplanteris *et al.* [123] in a group of healthy young men and women. The tomato supplementation led to an overall flow-mediated dilatation increase particularly in individuals with lower baseline values, and a decrease of total oxidative status past 15 days.

Recently, Vilahur *et al.* [12] reported that the intake of cooked tomato sauce protects against low-density lipoprotein-induced coronary endothelial dysfunction by reducing oxidative damage (diminished DNA damage in the coronary arteries), enhancing endothelial NOS (eNOS) expression and activity, and improving HDL functionality (associated with protein profile changes in apolipoprotein A-I (Apo A-I) and apolipoprotein J (Apo J)). The study was performed in pigs that received a hypercholesterolemic diet and a supplement of cooked tomato sauce (100 g, 21.5 mg lycopene) for 10 days.

Regarding *in vitro* studies, Armoza *et al.* [98] demonstrated the protective role of

lycopene and lutein in improving the basic endothelial function. The study was performed in two cultured endothelial cell models and it was verified an increase in the NO levels and a decrease in the endothelin (ET-1) release. Both carotenoids were efficient in attenuating the inflammatory NF-κB signalling, in particular decreasing the TNF-α-induced leukocytes adhesion, the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), and nuclear translocation of NF-κB components and some revert of the inhibitor of kappa B (IκB) ubiquitination. Furthermore, both compounds inhibited the NF-κB activation in transfected endothelial cells. This study demonstrated that the prevention of the overexpression of adhesion molecules through inhibition of NF-κB signalling may be one of the main mechanisms driving carotenoids to attenuate inflammatory leukocyte adhesion to endothelium.

**Tomato has Antitumour and Anticarcinogenic Properties**

Cancer is a very complex disease caused by cells without the usual control over growth. The apparent causes of this disease can diverge case by case; there are two classes of genes capable of controlling its development, namely oncogenes and tumour suppressor genes. Healthy cells follow a normal growth and proliferation pathway with a definite lifespan, whereas cells with an oncogenic activation undergo much faster division and have an indefinite lifespan. Generally, the cancer formation occurs when an oncogene and a tumour suppressor gene are activated and inactivated in a cell at the same time, respectively. The tumour suppressor genes are involved in the unregulated cell growth inhibition and caretaker genes control the rate of mutation in the genome. Thus, accumulation of mutation in the genome and consequent higher rate of tumour formation can be caused by a defective caretaker gene. Therefore, cancer arises due to functional deformities in multiple genes [107, 124]. Furthermore, the DNA damage by reactive species can also lead to increased risk of cancer.

In turn, degradation and penetration of the cell extracellular matrix by tumour cells under the action of matrix metalloproteinases (MMPs) and urokinase-type plasminogen activator (u-PA) are key steps in the metastatic cascade of cancer cells. MMPs are the most important proteases involved in tumour cell migration, spreading, tissue invasion and metastasis, and its expression is regulated by

extracellular signal regulating kinase (ERK1/2) and c-Jun N-terminal kinase (JNK) [125]. Among them, MMPs, MMP-2 and MMP-9 are key enzymes and are involved in metastasis processes [126]. Furthermore, the inhibition of the mitogen-activated protein kinase (MAPK) pathway (which is involved in signalling cascades) can prevent angiogenesis, proliferation, invasion and metastasis in many tumours [127, 128]. The metastasis process is also regulated by the phosphatidylinositide-3 kinase (PI3K)/Akt signalling pathway [129]. The NF-κB can also facilitate cell proliferation, angiogenesis and metastasis. This protein complex consists of a p50/p65 heterodimer that is masked by the inhibitor I kappa B alpha (IκBα), which causes its retention in the cytoplasm under resting conditions. The IκBα kinase can be activated by various stimuli, including those induced by TNF-α and LPS [95].

Tomato extracts and derived compounds have shown promising effects over different cancer cell lines. Stajčić *et al.* [9] investigated the cell growth activity of tomato waste extracts obtained from different tomato genotypes. Antiproliferative effects (determined by sulforhodamine B test) were observed in all cell lines (HeLa, MCF7 and MRC-5) at higher concentrations. The authors also correlated the carotenoids content with the antiproliferative and antioxidant activities.

Tang *et al.* [130] verified that low concentration of lycopene and eicosapentaenoic acid could inhibit in a synergistic way the proliferation of human colon cancer HT-29 cells. The inhibitory effects were, partly, associated with the down-regulation of the PI-3K/Akt/mTOR signalling pathway, known to play an important role in tumour progression. Therefore, the inhibition of this pathway is a promising approach for discovery of novel chemotherapeutic agents. More recently, Kim *et al.* [96] investigated the effect of α-tomatine on CT-26 colon cancer cells *in vitro* and *in vivo* in an intracutaneously transplanted mouse tumour. It was demonstrated that α-tomatine in pure form and in tomatine-rich green tomatoes might prevent colon cancer; α-tomatine induced about 50% lysis of the colon cancer cells at 3.5 μM after 24 h of treatment. It was also found that α-tomatine induced cell death through caspases-independent signalling pathways. Intraperitoneally administered α-tomatine also clearly inhibited tumour growth.

Prostate cancer is the second most common cause of male cancer death in the world [131]. A role for NF-κB in the progression of this cancer has been suggested; NF-κB is activated in androgen-insensitive prostate carcinoma cells, and overexpression of NF-κB p65 protein has been detected in the nuclear fraction of prostate cancer clinical specimens [132]. The chemopreventive potential of α-tomatine on androgen-independent human prostatic adenocarcinoma PC-3 cells was evaluated by Lee *et al.* [94]. The treatment with α-tomatine caused a concentration-dependent inhibition of cell growth. It was less cytotoxic to normal human liver WRL-68 cells and normal human prostate RWPE-1 cells. α-Tomatine exhibited its cytotoxic effects against adenocarcinoma PC-3 cells as early as one hour after treatment, which were assessed by the real-time growth kinetics. The glycoalkaloid α-tomatine induced apoptosis and inhibited NF-κB activation, as well as the activation of caspase-3, -8 and -9, suggesting the involvement of both intrinsic and extrinsic apoptosis pathways. Subsequently [95] it was shown that α-tomatine suppresses NF-κB activation through inhibition of IκBα kinase activity, which leads to sequential suppression of IκBα phosphorylation, IκBα degradation, NF-κB p65 phosphorylation, and NF-κB p50/p65 nuclear translocation. As indicated, α-tomatine was able to induce apoptosis; it reduced the TNF-α induced activation of the pro-survival mediator Akt, and the NF-κB inhibition caused a reduction in expression of NF-κB-dependent anti-apoptotic proteins. Moreover, intraperitoneal administration of this bioactive glycoalkaloid clearly attenuated the growth of PC-3 cell tumours (grown subcutaneously and orthotopically) in mice. These effects were accompanied by increased apoptosis, lower proliferation of tumour cells, and low nuclear translocation of the p50 and p65 components of NF-κB. Recently, Kolberg *et al.* [82] investigated whether tomato paste has the ability to modulate NF-κB activity and cancer-related gene expression in human prostate cancer cells (PC-3) and PC-3 xenografts. PC-3 cells were stably transduced with an NF-κB-luciferase construct and then treated with tomato extract or a placebo. Mice bearing PC-3 xenografts received a high-fat diet with or without 10% tomato paste for 6.5 weeks. The tomato extract considerably inhibited the TNF-α stimulated NF-κB activity in the PC-3 cells, and modulated the expression of genes associated with inflammation, apoptosis, and cancer progression. Mice fed tomato paste diet revealed accumulation of lycopene in liver, xenografts and serum. The tomato paste had no effect on tumour size in

mice; but there was a trend toward inhibition of NF-κB activity in the xenografts. Gene expression, most prominent in xenografts, was higher after tomato treatment.

Lung cancer is becoming increasingly common. About 40% of these cancers are adenocarcinoma, a type of non-small cell lung cancers with a low prognosis and highly potential for metastatic [133]. A study carried out by Yan *et al.* [126] examined the effect of tomatidine on the migration and invasion of human lung adenocarcinoma A549 cells. *In vitro* treatments with non-toxic doses of tomatidine resulted in markedly suppressed cell invasion, while cell migration was not affected. Tomatidine reduced the mRNA levels of MMP-2 and MMP-9 and increased the expression of reversion-inducing cysteine-rich protein with kazal motifs (RECK, a protein involved in the proteolytic degradation of extracellular matrix in tumour metastasis), as well as the tissue inhibitor of MMP-1. It also inhibited the ERK and Akt signalling pathways and NF-κB activity.

**Tomato Protects Liver from Hepatotoxicity and Hepatocarcinogenesis**

Oxidative damage caused by free radicals formed during the metabolism of nitrosamines has been suggested as one of the main cause for the initiation of hepatocarcinogenesis [134]. *N*-Nitrosamines are a class of chemical compounds that are metabolised to prooxidant and carcinogenic substances. *N*-Nitrosodieth--lamine is a representative of this class capable of generating carbocations and ROS during the cytochrome P450-mediated biotransformation. Liver injury induced by *N*-nitrosodiethylamine is a well-known model of hepatotoxicity commonly used for screening of hepatoprotective effects of natural matrices. A lycopene-enriched tomato paste tested by Kujawska *et al.* [103] was suitable for suppressing the *N*-nitrosodiethylamine-induced oxidative stress in rats. Pre-treatment with tomato paste protected antioxidant enzymes (SOD, CAT and glutathione reductase) and decreased the DNA damage in leucocytes and the plasma concentration of protein carbonyls. The microsomal lipid peroxidation was also decreased in liver of rats pre-treated with a lower dose of tomato paste. Gupta *et al.* [134] investigated the involvement of tomato lycopene against oxidative stress induced by the deleterious effect of *N*-nitrosodiethylamine on cellular macromolecules of mice, having been demonstrated the intervention of lycopene

on the initiation of carcinogenesis. Indeed, lycopene has influence on multiple dysregulated pathways during initiation of carcinogenesis; in particular it helps in the membrane fluidity normalization, improvement of antioxidant enzymes activity and reduction of glutathione (GSH) which accounted for reduced oxidative damage.

The antioxidant and hepatoprotective properties of naringenin and its β-cyclodextrin formulation at a dose of 50 mg per kg of body weight were evaluated by Hermenean *et al.* [102]. Serum-enzymatic and liver antioxidant activity and histopathological and ultrastructural changes were investigated in mice subjected to acute intoxication with carbon tetrachloride ($CCl_4$), one of the most potent hepatotoxins. The authors verified that both naringenin and naringenin/β-cyclodextrin complex have antioxidant and hepatoprotective effects against injuries caused by $CCl_4$. Particularly, 24 h after the $CCl_4$ administration, the activity of the transaminases aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and the levels of MDA were increased. A considerable decrease in SOD, CAT and GPx activities and in the GSH levels were also detected. Additionally, extended centrilobular necrosis, steatosis, fibrosis, and an altered ultrastructure of hepatocytes were also verified.

The primary liver cancer has become the fifth most common malignancy in the world [135]. Due to lack of early detection or screening biomarkers, its diagnosis is made at an advanced stage of the disease. Thus, the identification of potential risk factors for early hepatocarcinogenesis and the search for preventive and/or protective measures against them at an early stage are urgently needed. Growing evidence has associated hepatocellular carcinoma and nonalcoholic steatohepatitis (NASH), a chronic and often "silent" liver disease characterized by fat accum-ulation and infiltration of inflammatory cells in the liver [136]. Wang *et al.* [137] studied the efficacy of an equivalent dosage of dietary lycopene from either a pure compound or a tomato extract against NASH-induced hepatocarcino-genesis. In this study, rats were injected with diethylnitrosamine and then fed either a Lieber-DeCarli control diet or a high-fat diet with or without lycopene or tomato extract for 6 weeks. Both lycopene and tomato extract supplementations considerably decreased the number of altered hepatic foci, being expressed the placental form of glutathione-S transferase in the liver of rats that received a high-fat diet.

Decreased activation of NF-κB was verified. Both supplementations reduced the lipid peroxidation induced by the high-fat diet in the liver; it was observed also a significantly decreased inflammatory foci and mRNA expression of proinflammatory cytokines (TNF-α, IL-1β and IL-12) in the group that received a high-fat diet and the tomato extract. Thus, it was concluded that lycopene and tomato extract inhibit the NASH-induced hepatocarcinogenesis mainly as a result of reduced oxidative stress.

Given the beneficial effect of antioxidant supplementation in metal-induced toxicity, and concerns regarding the benefits of tomatoes on different target tissues, Nwokocha *et al.* [138] elucidated the effect of tomato extract on reducing the accumulation of heavy metal in the liver of rats. The tomato extract administration was beneficial in reducing heavy metal accumulation in the liver, namely reducing uptake and enhancing the elimination of these metals in a time dependent manner. The hepatoprotective effect against cadmium toxicity was very high. Among the tomato bioactive compounds, vitamin C has been reported to decrease liver damage from cadmium, mercury and lead [139, 140].

## SAFETY PRECAUTIONS

*Solanum* is probably the most economically important genus, containing familiar crop species, as well as many species containing poisonous or medicinally useful secondary compounds. Because of this, the tomato plant was long used only for ornamental purposes [1]. However, there are no reports of any toxic effect caused by the consumption of tomato fruit, but some reports correlate potato glycoalkaloids with noxious effects in humans. Potatoes with high levels of glycoalkaloids can severely affect the consumer health or even cause death. Mild poisoning cases can cause headache, vomiting and diarrhea. Some neurological symptoms have also been described, namely drowsiness, visual disturbances, apathy, hallucinations, mental confusion, dizziness, trembling and restlessness [89]. Thus, to ensure safety to consumers, it is necessary to perform further studies of toxicity and bioavailability of the tomato glycoalkaloids considering different maturation stages. Besides glycoalkaloids, other antinutritional and potentially harmful compounds, such as oxalic acid [141] and nitrate [142], have been detected in different concentrations in tomato samples.

## INDUSTRIAL APPLICATIONS

Despite the undeniable importance of tomato in the food processing industry, this fruit as well as its by-products can have other applications on biotechnology, chemical, pharmaceutical, and cosmetic industries. Industrial tomato by-products contain significant amounts of the bioactive compounds endowed with different bioactivities and important health promoting effects, as reported in this chapter [143]. Therefore, as tomato wastes are bioorganic materials and being in line with the trend for sustainability, these value-added molecules can be isolated to be used as natural bioactive ingredients for different industries. Extracts or isolated compounds from tomato by-products can also be used as anti-inflammatory, cardioprotective, anticholesterolemic, antidiabetic, and antitumour agents to develop new products and drugs. The isolated compounds can also be applied in the food industry to develop new functional foods and nutraceuticals, and used as food additives to extend their shelf-life.

## CONCLUDING REMARKS

Tomato is the second most consumed vegetable worldwide, thus being an important source of nourishment for the world's population. This fruit is a dietary source of carotenoids (mainly lycopene), vitamins and phenolic compounds (hydrocinnamic acids and flavonoids) which contribute to its health-promoting effects. Unripe (green) tomatoes also contain glycoalkaloids (α-tomatine), compounds endowed with important bioactive properties. Several *in vitro* and *in vivo* studies carried out in the last years confirm the assigned health-promoting effects to tomato, whether as a processed food, extract or it isolated compounds. These studies highlight its antioxidant and anti-inflammatory effects which, mainly *via* down-regulation of NF-κB and proinflammatory mediators such as cytokines, protect from cardiovascular diseases (avoiding the endothelial dysfunction) and various types of cancer (through the modulation of oncogenic signalling pathways). At the same time, epidemiological studies support the health benefits of the consumption of tomatoes and tomato-based foods. Therefore, this "superfruit" has been considered as a functional and powerful disease-fighting food involved in the prevention of chronic degenerative diseases. However, further studies are necessary to clarify some points related to the bioaccessibility

and bioavailability of some bioactive compounds and inherent mechanisms of bioactivity, as well as to evaluate synergistic effects among different compounds in various cell lines and animal models, and optimize extraction conditions of value-added compounds from tomato by-products for industrial applications.

## CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

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